Rare case of eosinophilic granulomatosis with polyangiitis in two patients with α-1-antitrypsin deficiency (PiSZ)

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TITLE OF CASE

A Rare Case of Eosinophilic Granulomatosis with Polyangiitis in two patients with Alpha-1Antitrypsin Deficiency (PiSZ).

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SUMMARY Up to 150 words summarising the case presentation and outcome

We present two cases of eosinophilic granulomatosis with polyangiitis occurring with alpha-1antitrypsin deficiency, both PiSZ phenotype. The simultaneous occurrence of these two conditions has seldom been described in the literature, despite evidence of an association between alpha-1-antitrypsin deficiency and other forms of vasculitis. Both patients had pulmonary involvement and reported intermittent exacerbations of vasculitic symptoms. Both patients were managed on low dose oral steroids and azathioprine remaining well with occasional exacerbations. It is important to consider whether there is an association between eosinophilic granulomatosis with polyangiitis and alpha-1-antitrypsin deficiency, as this may lead to more severe pulmonary symptoms during exacerbations. If a genetic association between the two conditions is found, clinicians should be aware of the possible need to screen for alpha-1antitrypsin deficiency in appropriate patients.

BACKGROUND Why you think this case is important – why you decided to write it up

Eosinophilic granulomatosis with polyangiitis (EGPA), formerly known as Churg Strauss syndrome, is a rare systemic inflammatory disease of small and medium-sized blood vessels. It is associated with eosinophilia, asthma and damage to the skin, nerves, lungs, kidneys and heart due to vasculitis.[1,2] No widely accepted diagnostic criteria currently exists for EGPA, though a number of classification criteria are available.[3,4] Alpha-1-antitrypsin deficiency (AATD) is a common but under-diagnosed genetic disorder that causes relative deficiency of the liver enzyme antitrypsin, which protects the lung against proteinases. AATD is caused by mutations in the SERPINA1 gene located on the long arm of chromosome 14 (14q31-32.3), which are inherited in an autosomal codominant manner.[5,6] The highly polymorphic nature of this gene means that over 90 protein variants (known as PI* types) have been identified.[7]

The deficiency phenotypes PI*SZ and PI*ZZ are associated with greater severity of disease in AATD.[8] An association between AATD phenotype and a number of forms of vasculitis has been outlined in the literature. Both Mahr and Morris and colleagues identify an association between carriage of the Z deficiency allele and granulomatosis with polyangiitis (GPA), also known as Wegner's granulomatosis.[9,10] Mahr and colleagues concluded that both SZ and ZZ phenotypes increased the risk of GPA in AATD.[9] Both alleles are over-represented in patients with anti-neutrophil cytoplasmic antibodies (ANCA)-associated vasculitis compared to normal populations.[9,11] ANCA positive status is found in many vasculitic syndromes including EGPA.[2] Therefore, it is possible that a number of EGPA patients may express S and Z deficiency alleles, as part of undiagnosed AATD. Here we present two such cases, with both patients expressing PI*SZ AATD phenotypes in conjunction with EGPA.

CASE PRESENTATION Presenting features, medical/social/family history

Patient 1. An 82 year old Caucasian female presented to hospital with a two-week history of lethargy, shortness of breath, anorexia, back pain, myalgia and paraesthesia in the arms and legs. She had noticed a mottled, red rash on the medial aspect of her left leg a week previously, which had resolved prior to presentation. The patient had been diagnosed with asthma 30 years previously, later being diagnosed with chronic bronchitis and alpha-1-antitrypsin deficiency (PI*SZ

type). She is a lifelong non-smoker. On inspection, there were no skin changes identified, the chest was clear on auscultation and heart sounds were normal with no added sounds. On abdominal examination, there was mild tenderness in the epigastric and umbilical regions. On examination of the peripheral nervous system, there was normal tone, power, sensation, reflexes and coordination in both the upper and lower limbs. After initial assessment the clinical suspicion was of an underlying malignancy.

Patient 2. A 36 year old Caucasian woman was admitted to hospital with a 6-week history of increasing dyspnoea, cough, fatigue, palpitations, back pain and night sweats. Recently she had suffered with persistent nausea and had lost weight. There was pain in her elbow joints, there were no other changes to her joints or skin. She had a past medical history of post-natal jaundice, juvenile arthritis, perennial rhinitis, chronic sinusitis, hay fever, endometriosis and late onset asthma. She had a paternal second cousin with haemachromatosis and maternal second cousin Wegener's Granulomatosis. She took salbutamol as required and beclomethasone inhalers for her asthma. She was a non-smoker. On examination, patient was tachycardic and appeared considerably short of breath at rest. Auscultation of the chest was clear and general examination was normal apart from a low grade pyrexia.

INVESTIGATIONS If relevant

Patient 1. Blood tests revealed an unusually high eosinophil count of 24.4x109/L, deranged liver function tests; ALP 255U/L, ALT 45U/L, raised inflammatory markers; white cell count (WCC) 37.4x109/L, C-reactive protein (CRP) 105mg/L. Creatinine kinase was 330U/L. Serology showed positive anti-nuclear antibodies (ANA), positive anti-nuclear antibodies (ANCA), titre = 1/50, (pANCA or cANCA pattern unknown), negative myeloperoxidase antibodies (MPO) and negative proteinase 3 antibodies. Her alpha-1-antityrpsin level was 0.83µM. A CT of the thorax, abdomen and pelvis showed bilateral apical scarring and small hilar and mediastinal calcified lymph nodes but no other obvious abnormalities.

Patient 2. Resting saturation was 93-96%, peak flow was 450 L/min and FEV1/FVC ratio had reduced from 2.6/2.7L to 2.15/2.2L. Serum testing demonstrated raised WCC; 15.9x109/L and raised eosinophils; 5.6x109/L with neutrophils of 7.6x109/L. Liver function was mildly deranged ALP 121U/L, ALT 42U/L and erythrocyte sedimentation rate (ESR) was markedly raised at 103mm/hr. Serology showed negative ANCA. Sputum cultures, thyroid function tests, urea and electrolytes were normal.

Urinalysis showed a trace of blood and protein but no haematuria. A chest X-ray showed significant bilateral patchy infiltrates, particularly of the upper lobes with a slightly prominent left hilum. Bronchoscopy and transbronchial biopsy was inconclusive.

DIFFERENTIAL DIAGNOSIS If relevant

TREATMENT If relevant

Patient 1. The patient was treated with three doses of intravenous methylprednisolone 500 mg and a prolonged reducing course of oral prednisolone, with the option of introducing intravenous cyclophosphamide if symptoms did not resolve. On review in clinic two weeks after discharge, the majority of her symptoms had resolved, aside from mild residual paraesthesia in the fingers and toes. Her Birmingham Vasculitis Assessment Score had improved from 15 to 0 and the eosinophil count had normalised from 24.4 to 0.2. Intravenous cyclophosphamide was therefore not required and the patient was started on azathioprine at a dose of 2 to 3mg/kg, for up to five years.

Patient 2. The patient was managed with oral prednisolone. This led to a rapid improvement in symptoms, serum tests normalised, aside from liver function which remained slightly deranged. The patient was started on long-term, low dose prednisolone 5mg OD and azathioprine 75mg OD. On review in clinic two weeks later, a diagnosis of EGPA with pulmonary and sinus involvement was made.

OUTCOME AND FOLLOW-UP

Patient 1. Eighteen months on from her initial presentation, the patient reported marked symptomatic improvement. Prednisolone was continued for 18 months and gradually stopped. She remains on azathioprine alone, at a dose of 100mg OD. On review, the patient reports regular exacerbations of her respiratory symptoms, occurring approximately every two months, with worsening cough, production of white sputum, worsening shortness of breath and reduced exercise tolerance from 300 yards to 100 yards on the flat. Patient is managed by her General Practitioner for the mainstay and exacerbation symptoms are generally treated with antibiotics which appeared to improve her symptoms but not fully resolve them.

Patient 2. Twenty years following her first presentation of vasculitis, the patient presented to the specialist Alpha-1-Antitrypsin Deficiency clinic with a diagnosis of PI*SZ alpha-1-antirypsin deficiency, identified through family screening. At the time of review, the patient was well and had unremarkable examination findings. The most recent serology showed an eosinophil count of 0.3x109/L and normal inflammatory markers, IgE 9 ku/L, negative ANA, negative ANCA, weakly positive smooth muscle antibodies and normal liver function. The most recent imaging showed no evidence of emphysema on CT thorax.

Patient 2 remains under the care of a specialist rheumatology team whom she sees regularly and during exacerbations. She reports a baseline of persistent fatigue with mild exacerbation of the vasculitis once yearly on average. Exacerbations are typified by gradually increasing fatigue followed by cough with minimal white sputum and increasing shortness of breath. Low grade fever, nausea, joint and back pain, and palpitations are also common features of her exacerbations. Sinus symptoms include pain, headache and serous yellow discharge with occasional bloody discharge. Patient 2 adopts a largely self-management strategy with mild exacerbations, she checks for reversibility in peak flow to salbutamol and tests her urine for blood and protein. If peak flow demonstrates no reversibility and her urine dip is positive for blood and protein, she manages this by increasing prednisolone to 20 or 30mg for up to three days and then continues or titrates down depending on response. She also seeks advice from her General Practitioner or Rheumatologist.

DISCUSSION including very brief review of similar published cases (how many similar cases have been published?)

Here we describe the rare occurrence of eosinophillic granulomatosis with polyangiitis in two patients with PI*SZ alpha 1-antitrypsin deficiency. In this case series, both patients presented with distinctive clinical features of EGPA. Both meet four out of six criteria for classification of EGPA according to ACR: asthma, eosinophilia >10%, neuropathy, non-fixed pulmonary infiltrates, paranasal sinus abnormalities, extravascular eosinophil infiltration on biopsy.[3] In the absence of validated diagnostic criteria, the ACR classification is useful for the consideration of essential characteristics for EGPA, however it is important to underline that this classification is not designed as diagnostic criteria.[4] Since our patients exhibited the majority of classification criteria, and in both cases had their diagnosis given to them by an appropriate specialist (rheumatologist) we believe the diagnosis of EGPA is accurate, but acknowledge that certainty is difficult in the absence of specific criteria

against which to judge. A particularly desirable investigation might have been histology, which was inconclusive in patient 2.

Investigations demonstrated markedly high eosinophils with raised inflammatory markers in both cases. Both patients, though diagnosed twenty years apart, have been treated successfully with high-dose steroids and azathioprine, though exacerbation symptoms manifest intermittently in both. As a rare and complex condition it is important to highlight the importance of specialist input into the management of patients with EGPA. In this case series patient 1 is largely managed by the GP and patient 2 has over time adopted a supervised self-management approach. The role of the specialist team is fundamental to safe and expert management of this complex chronic disease. Failure to involve specialists in the ongoing care of such patients is expressly discouraged.

The coexistence of AATD and vasculitis is shown to be strongly associated with expression of the Z deficiency allele.[11,12] In such cases, patients are often positive for anti-proteinase 3 (PR3) antibodies and cANCA, a characteristic feature of GPA.[11,12] Evidence has also shown that expression of the S deficiency allele may be associated with other forms of vasculitis.[7] PI*SS or PI*SZ patients demonstrate a tendency to be pANCA positive.[7] pANCA positive status is often found in conjunction with positive anti-myeloperoxidase (MPO) antibodies; this occurs in approximately 40% of EGPA cases[2,3,4] such that the majority of EGPA patients, like our presented cases, do not exhibit anti-MPO antibodies. Nevertheless, an association between EGPA and AATD may exist and the occurrence of EGPA in the two PI*SZ AATD patients described raises two questions; is there an association between the PI*SZ phenotype and vasculitis, and is this distinct from the association already established between ANCA positive vasculitis (GPA) and PI*ZZ? The generalised nature of vasculitis symptoms, and indeed of AATD, may mean that diagnosis is missed initially and biochemical investigations are required; these eventually led to diagnosis in our presented cases. Clinicians should therefore consider the possibility of AATD as a possible causative or exacerbating factor in EGPA, particularly when the vasculitic presentation is severe or accompanied by additional signs of AATD. Given the strength of evidence for an association between AATD and other forms of vasculitis, mainly GPA, further investigation into the association between AATD and EGPA is warranted. If additional evidence were to emerge in support of an association between AATD and EGPA, it would strengthen the argument for early screening.

It is also interesting to speculate whether AATD would alter the management of vasculitis. Specific therapy for AATD does exist, in the form of intravenous supplementation of AAT, known as augmentation therapy. This treatment may slow the progression of emphysema [Chapman et al, Lancet Resp Med (2015)] and is also an accepted way to manage episodes of panniculitis [Blanco et al, OrphaNet J Rare Dis (2011)]. A single case of concurrent vasculitis and PiZZ AATD has also been reported where the vasculitis responded to augmentation therapy [Dowd et al, J Am Acad Derm (1995)], though this did not appear to be a case of EGPA. The role of augmentation in vasculitis unrelated to AATD is unclear; theoretically it might limit the damage from neutrophil elastase release in the inflamed vasculitic areas. Indeed AAT activity has been shown to be low in vessel walls of GPA patients [Mota et al, Rheumatol Int (2014)], thus giving a rationale for use of AAT augmentation in this condition. However there have been no reports of such management in the literature to our knowledge, thus this also remains an area for future research.

LEARNING POINTS/TAKE HOME MESSAGES 3 to 5 bullet points

• Eosinophilic granulomatosis with polyangiitis (EGPA) is a systemic inflammatory condition which affects multiple organs.

• Eosinophilia and asthma are both associated with EGPA.

• Presenting symptoms may be non-specific but marked eosinophilia and raised inflammatory markers should raise the suspicion of EGPA.

• Alpha 1 antitrypsin deficiency has previously shown an association with vasculitis.

• More research is required to determine whether there is an association between the PI*SZ phenotype and EGPA.

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